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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,335	01/10/2006	Cornelis Marius Timmers	2002.749US	8737

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EXAMINER	
BLAND, LAYLA D	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
12/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,335	TIMMERS ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 3, 2008 has been entered.

This Office Action is in response to Applicant's request for continued examination (RCE) filed October 3, 2008, the declaration of Cornelius Marius Timmers filed October 3, 2008, and response to the Final Office Action (mailed February 20, 2008), filed October 3, 2008.

Claims 1-8 and 11 are pending and are examined on the merits herein.

The following are new or modified rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a particular example of the claimed compounds as contraceptives in females (will be discussed below), is not enabling for other compounds as such, is not enabling for "fertility regulation" in either males or

females, is not enabling for the use of the claimed compounds as contraceptives for males, and is not enabling for compounds other than those discussed in the declaration of Cornelius Marius Timmers filed October 3, 2008. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the genus of compounds shown in claim 1 and the use of those compounds in a method of "fertility regulation." The specification does not explicitly define "fertility regulation," but states that the claimed compounds may be used for treating infertility or for contraception. Formula I includes the variables R3 and R4, which include heteroaryl and aryl groups, which can be further substituted with phenyl groups, which in turn may be further substituted, etc. Thus, the claims taken together with the specification imply that all compounds encompassed by the genus of claim 1 may be used as contraceptives and for treating infertility.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Van Straten et al. (J. Med. Chem. 2005, 48 (6), 1697-1700) teach that certain molecules sharing the same core as those of claim 1 are antagonists for the follicle stimulating hormone receptor, inhibit follicle growth and ovulation in an ex vivo mouse model, and may be useful as contraceptives [see abstract]. Of the van Straten compounds which share the same core as Formula I, none were described as agonists.

The prior art teaches that small molecule FSHR antagonists are of interest as contraceptives for women, but their use as contraceptives for men is uncertain. Guo (Expert Opin. Ther. Patents (2005) 15(11)) teaches that compound 24 [shown on page 1561, Figure 3] has been shown to inhibit ovulation in female rats, "bolstering confidence" that such compounds could be used as contraceptives for women (this teaching refers to the van Straten publication previously mentioned). However,

"whether FSHR antagonists could be effect contraceptives for men is still of debate" [page 1562, second column, first paragraph].

The prior art also teaches that the activity of FSHR antagonists changes significantly with structural modifications. van Straten et al. teach that introduction of a 4-chlorophenylcarbonyl group at position 6 of compound 4 induced a switch from micromolar full agonistic activity to nanomolar full antagonistic activity [page 1697, last paragraph]. Aromatic substituents at position 6 are preferred, but space is limited because introduction of a t-butyl group led to a dramatic drop in potency [page 1698, first paragraph.

Guo et al. also review a number of FSHR agonists which are claimed to be useful for contraception and fertility treatment [page 1560, section 2.4]. However, none of these compounds are structurally similar to the claimed compounds and no guidance is provided as to whether molecules similar to the claimed molecules might be effective *in vivo* for fertility treatment.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification and declaration of Cornelius Marius Timmers filed October 3, 2008 has provided data indicating that several compounds of Formula (I) are antagonists of the FSH receptor, a few are agonists of the FSH receptor, and two can be either depending on concentration. Clearly, based on this data, the activity is specific for each compound and is not predictable. Furthermore, Formula I includes variables which can be substituted with other variables, which in turn can be substituted

with other variables, etc., resulting in a large number of very complex molecules encompassed within Formula I. van Straten et al. teach that even small structural modifications such as the addition of a single alkyl group can result in significant changes to the activity of the compounds. Finally, there is no guidance or working examples in the specification for the use of the claimed molecules *in vivo*. There is some evidence in the cited references that van Straten's compound 10 (same as compound 24 in Guo) may be effective for contraception in females. However, the cited references also clearly state that, absent such evidence, the *in vivo* usage of FSHR agonists and antagonists is not predictable. For instance, van Straten teaches "substituted 6-amino-4-phenyltetrahydroquinoline derivatives…may serve as starting points for further optimization to evaluate the feasibility of FSH receptor antagonists as a novel method for contraception." Guo states that "only in the clinic will the question of whether small molecule LHR and FSHR modulators will be successful as fertility regulating agents be answered."

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the unpredictable activity of the claimed compounds and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Response to Arguments

Applicant argues that the specification provides guidance for assays to determine the activities of compounds of Formula I, and thus is enabled for "fertility regulation." This argument is not persuasive because Applicant has not shown that compounds having said activity can be used for "fertility regulation." The cited references clearly show the state of the art, which states that even compounds showing a particular activity *in vitro* are considered questionable targets for clinical use. Furthermore, in order to practice the invention across the full scope of the claims, the skilled artisan would be required to synthesize an infinite number of compounds, as Formula I is open-ended to substitutions, carry out the assays mentioned by Applicant to determine activities of each the compounds, and then address the problem of *in vitro* versus *in vivo* correlation for each of the compounds, which would involve establishing effective treatment regimens for both fertility treatment and contraception, in both males and females, including proper dosages and routes of administration, in animal models and clinical trials. For these reasons, it is considered that the skilled artisan would be burdened with undue experimentation to practice the full scope of the invention as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 13, and 16 of copending Application No. 10/540,336. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in each application are drawn to very similar genera of compounds. The genera differ in the presence or absence of one substituent on the bicyclic ring. It is also noted that the compounds of copending Application No. 10/540,336 are described as having the same utility as the instantly claimed compounds and species which meet the limitations of the instant claims are present in the specification of copending Application No. 10/540,336.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Bland/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623